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10/581,757	03/02/2007	Shinji Yamasaki	SHIM-018	7036

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EXAMINER	
CARLSON, KAREN C	
ART UNIT	PAPER NUMBER
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/581,757	YAMASAKI ET AL.	
	Examiner	Art Unit	
	Karen Cochrane Carlson, Ph.D.	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *6-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6 of them*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Applicant's election without traverse of Group 1, Claims 1-5 drawn to polynucleotide encoding SEQ ID NO: 2 and polypeptide having SEQ ID NO: 2 (CdtA derived from C. coli), in the reply filed on June 27, 2008 is acknowledged.

Claims 1-30 are currently pending. The Examiner has withdrawn Claims 6-30 from further consideration because these claims are drawn to non-elected inventions. Claims 1-5 as drawn to polynucleotide encoding SEQ ID NO: 2 and polypeptide having SEQ ID NO: 2 (CdtA derived from C. coli), are currently under examination.

For examination/art purposes, Claim 1 is taken to read as:

A polynucleotide encoding a cytolethal distending toxin, which is any one of:

(a) a polynucleotide encoding a polypeptide comprising the amino acid sequence SEQ ID NO: 2;

(b) a polynucleotide comprising the nucleotide sequences of position 1 to 777 of SEQ ID NO: 1;

(c) a polynucleotide encoding a polypeptide comprising an amino acid sequence with a substitution, deletion, addition, and/or insertion of one or more amino acids in SEQ ID NOs: 2; or

(d) a polynucleotide that hybridizes under a stringent condition to DNA comprising the nucleotide sequences of position 1 to 777 of SEQ ID NO: 1.

The disclosure is objected to because of the following informalities: the specification refers to documents and not to specific references. Without the IDSs in hand, which will not be included in an issued patent, one skilled in the art cannot know

which references are attributed to the statements in the specification. Applicants should resubmit the specification with the correct citation in place throughout.

Appropriate correction is required.

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Benefit of priority is to the filing of the Japanese Application filed December 5, 2003.

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-5 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The polynucleotide and polypeptide are not stated to be isolated and therefore read on these products in nature.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which.

Claims 1-5 comprise non-elected subject matter and therefore do not particularly point out and distinctly claim the subject matter which the applicant regards as his elected invention.

In Claim 1d, the stringency condition for the hybridization is not set forth. Also of note, the hybridizing nucleic acid must encode a cytolethal distending toxin and therefore primers are excluded from this portion of the claim.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form applicant regards as the invention the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5 are rejected under 35 U.S.C. 102(a or b) as being anticipated by Bang et al. (June 2003; PCT detection of seven virulence and toxin genes of *Campylobacter jejuni* and *Campylobacter coli* isolates from Danish pigs and cattle and cytolethal distending toxin production of the isolates. J. Applied Microbiology, 94(6): 1003-1014).

Bang et al. teach *C. coli* comprising the *cdtA* gene encoding CdtA. Specifically, Bang et al. identified the *cdtA* gene using primers GNW and IVH designed for use in *C. jejuni* (See Table 2 at page 1007; page 1008, left col, lines 7-9). These primers amplify a 164 nucleotide portion of the *cdtA* gene that encodes amino acids 134-188 of the

CdtA protein having SEQ ID NO: 2 (see the discussion below). The cell-free supernatants of the *C. coli* isolate were used to demonstrate that the *C. coli* secreted cell distending toxins (CDTs) in three different assays (page 1008, right col., to page 1009).

Therefore, Bang et al. teach a polypeptide comprising SEQ ID NO: 2 in the supernatant, and encoded by the cdtA gene of *C. coli* comprising nucleotides 1-777 of SEQ ID NO: 1 (**Claim 4**) because the *cdtA* gene is found in the *C. coli* and would inherently comprise nucleotides 1-777 of SEQ ID NO: 1. The secreted CTDs would include CdtA protein from the *C. coli* and that was found to be active in three different toxin assays.

The 164 polynucleotide sequence amplified by Bang et al. is a polynucleotide that encodes a polypeptide having N and C-terminal deletions of SEQ ID NO: 2, and the CdtA polypeptide of the *C. jejunis* is a polypeptide having substitutions, deletions, additions, and/or insertions of one or more amino acids of SEQ ID NO: 2 (**Claim 1**).

Because the polynucleotide of Claim 1 is not isolated, the *C. coli* genome is a vector comprising the polynucleotide encoding CdtA (**Claim 2**), and the *C. coli* itself is a host cell containing the polynucleotide encoding CdtA (**Claim 3**). The *C. coli* was cultured, the CdtA expressed, and supernatents comprising CdtA collected therefrom (**Claim 5**).

Applicant cannot rely upon the foreign priority papers to overcome this rejection under 102(b) because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Discussion of Prior Art:

It appears that there is a lot of art swirling around the *C. coli* CTDs, but at this time the Examiner has not been able to find a clear teaching or motivation or predictability regarding the *cdtA* gene or encoded protein from *C. coli*.

Pickett et al. (1996; Prevalence of cytolethal distending toxin production in *Campylobacter jejuni* and relatedness of *Campylobacter* sp. *cdtB* genes. Infection and Immunity 64(6): 2070-1078) teach the nucleic acid sequence encoding the entire cdt gene cluster in *C. jejuni* in Fig. 3. The predicted amino acid sequence for CdtA, CdtB, and CdtC are included in Fig. 3. In Fig. 2, Pickett et al. compares the amino acids sequences of *C. jejuni* with the amino acids of CdtA, B, and C of *E. coli.* Picket et al. teach that the *cdt* genes between *C. jejuni* and *E. coli* are related but are not highly homologous, with the highest homology being 59% identity in the 5' half of the *ctdB* gene (page 2074, left col., para. 1, line 10+). Pickett et al. teach that the overall level of amino acid sequence identity between the *E. coli* CdtA protein and the *C. jejuni* CdtA protein is a modest 34%, wherein 21% of the 268 amino acids are identical and 13% are conserved (page 2074, right col., line 3). Therefore, one skilled in the art would not know how highly conserved the nucleic acid and amino acid sequence between either the *ctdA* gene or CdtA protein of *C. jejuni* or *E. coli* with *C. coli* to predictably make

primers that would encode the CdtA protein of *C. coli* because Pickett et al. shows that here is low identity between the cdtA gene and encoded protein between *C. jejuni* and *E. coli*.

Bang et al. (June 2003b; PCR detection of seven virulence and toxin genes of *Campylobacter jejuni* and *Campylobacter coli* isolates from Danish pigs and cattle and cytolethal distending toxin production of the isolates. J. Applied Microbiology, 94(6): 1003-1014), as cited above, use the primers GNW and IVH designed for use in *C. jejuni* (See Table 2 at page 1007; page 1008, left col, lines 7-9) to detect the *cdtA* gene in *C. coli*. These primers amplify a 164 nucleotide portion of the *cdtA* gene that encodes amino acids 134 to 188 of the CdtA protein having SEQ ID NO: 2. Review of Pickett et al. show that these primers are found at nucleotides 540-563 and 684 to 704 of the nucleotide sequence encoding *C. jejuni* CdtA. Perusal of instant SEQ ID NO: 1 show that these primers are found at nucleotides 400 and 564 (reversed), encoding amino acids 134 to 188 of SEQ ID NO: 2). Therefore, Bang et al. did not have in hand the ORF encoding *C. coli* CdtA protein, but only a portion thereof.

Additionally, Bang et al. teach that *C. coli* CDTs were produced in low to no amounts (1009, left col) and that the activity was weaky positive (Table 4). See also Bang et al. (2001a; Prevalence of cytolethal distinging toxin (CDT) genes and CDT production in *Campylobacter* spp. isolated from Danish broilers. J. Med. Microbiol. 50: 1087-1094) which states that *C. coli* produced lower to non-detectable levels of toxin (abstract); Eyigor et al. (1999a; Detection of cytolethal distending toxin activity and *cdt* genes in *Campylobacter* spp isolated from chicken carcasses. Applied and

Environmental microbiology. 65(4): 1501-1505) who state that *C. coli* produces little or no toxin (abstract); and Eyigor et al. (1999b; Cytolethal distending toxin genes in *Campylobacter jejuni* and *Campylobacter coli* isolates: Detection and analysis by PCR. J. Clinical Microbiology. 37(5): 1646-1650) who show that *C. coli* isolates had CDT titers lower than 5 and do not appear to contain much CDT activity (page 1647, left col, 5 lines from the bottom. Therefore, motivation to isolate the DNA encoding *C. coli cdt* genes and encoded toxins is lacking.

The Examiner suggests the following claims:

31. (new) An isolated and purified polynucleotide encoding a cytolethal distending toxin, said polynucleotide selected from the group consisting of:

(a) a polynucleotide encoding a polypeptide comprising the amino acid sequence SEQ ID NO: 2; or

(b) a polynucleotide comprising the nucleotide sequences of position 1 to 777 of SEQ ID NO: 1.

32. (new) A vector comprising the polynucleotide sequence of Claim 31.

33. (new) a host cell comprising the polynucleotide of Claim 31 or the vector of Claim 32.

34. (new) A method for producing a cytolethal distending toxin, said method comprising culturing the host cell of Claim 33 and collecting the cytolethal distending toxin from the host cell or the culture supernatant.

It appears that the isolated protein is taught by Bang et al., for example. That is, the specific amino acid sequence SEQ ID NO: 2 only further characterizes the prior art protein. However, if there is evidence that the *C. coli* serotype CdtA sequences of Bang et al. differ from SEQ ID NO: 2, the following claim may be included:

35. (new) An isolated and purified cytolethal distending toxin, said polynucleotide selected from the group consisting of:

(a) a polypeptide comprising the amino acid sequence SEQ ID NO: 2; or

(b) a fragment of a polypeptide comprising the amino acid sequence of SEQ ID NO: 2, said fragment having cytolethal distending toxin activity.

NOTE, while proposed Claim 35 read over the art of record, Applicants may not have written description for fragments because no fragments have been made of SEQ ID NO: 2. If Applicants do have written description for fragments, please point this out in your response to this Office Action.

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Cochrane Carlson, Ph.D. whose telephone number is 571-272-0946. The examiner can normally be reached on 7:00 AM - 4:00 PM, off alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax

phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Karen Cochrane Carlson, Ph.D./
Primary Examiner, Art Unit 1656